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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Arne Elof Brändström

Serial No. : 640,020 Examiner: J. Fan

Filed : August 10, 1984 Group Art Unit: 121

For : NOVEL COMPOUNDS

DECLARATION UNDER RULE 132

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R :

I, Åke Gunnar Pilbrant, declare that:

1. I am a citizen of Sweden, residing at Snödroppevägen 6, S-434 00 Kungsbacka, Sweden.

2. I was awarded the degree of Master of Science in Pharmacy in 1965, and the degree of Farmacie Licenciat in 1969.

3. I was employed by AB Kabi, Stockholm, Sweden from 1969-1979 as Head of the Section for Development of Nonparenteral Dosage Forms, Department of Pharmaceutics. I have been employed by AB Hässle: Mölndal, Sweden from 1979 to the present as Head of the Section for Product Development, Gastrointestinal Products. I am the author or co-author of about fifteen papers in the field of pharmaceutical chemistry, pharmacy, biopharmacy and pharmacokinetics.

4. I am familiar with the U.S. Patent Application Serial No. 640,020 of Brändström, and with the Official Action dated January 2, 1985, in which the claims of the application were rejected.

5. I have caused a number of tests to be run to compare the stability of base addition salts of omeprazole with neutral omeprazole under two different storage conditions.

6. Sodium, calcium and magnesium salts of omeprazole were prepared according to the method described in U.S. Patent Application Serial No. 640,020. Samples of these salts, and of neutral omeprazole were placed in amber glass bottles, sealed with snap-cap polyethylene closures, and stored at 50°C. A second set of samples were placed in open petri dishes and stored at 37°C and 80% relative humidity.

7. Samples were withdrawn from each test container at time zero, and after 1, 3 and 6 months of storage. Magnesium and calcium salts were analyzed after 1.5 months rather than 1 month of storage.

8. The withdrawn samples were made into solutions containing 0.12 mg/ml of omeprazole by extraction with 25.0 ml of ammonia-methanol solution (6.0 ml conc. ammonia diluted to 100 ml with methanol) diluted to 1 liter with methylene chloride. The solutions were analyzed by HPLC using the extraction solvent as the mobile phase to determine the amount of degradation products.

9. Degradation of omeprazole was determined from the amount of degradation products found and is shown in the Table for each of the compounds tested. These results clearly demonstrate that all of the base addition salts are substantially more stable than neutral omeprazole for long term storage.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent thereon.

Dated: July 4, 1985

Åke Gunnar Pilbrant

ÅKE GUNNAR PILBRANT

Table

Total amount of by-products found after storage of omeprazole and omeprazole salts. The results are given as percent of intact omeprazole (peak area percent)

Storage time, months	Storage conditions °C/% r.h.	Omeprazole	Omeprazole sodium salt	Omeprazole magnesium salt	Omeprazole calcium salt
0	-	0.2	0.1	0.2	0.2
1*	+50	0.2			
	+37/80	0.2	0.1	0.3	1.5
3	+50	1.0	0.1	0.4	0.9
	+37/80	0.3	0.8	0.4	1.7
6	+50	>4	0.1	0.6	1.1
	+37/80	>6	1.2	0.7	1.7

*The magnesium and calcium salts were analysed after 1.5 months storage.